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13. ABSTRACT *(Maximum 200 words)*

This study assesses magnetic resonance (MR)-guided interstitital laster photocoagulation (ILP) for the treatment of breast cancer. ILP has been successfully used for the treatment of a variety of solid tumors, and recent studies have indicated the capability of ILP, which employs low level heat (~50°C) for about 10 minutes, to kill breast cancer tissue. As breast cancer cells are often interspersed with surrounding normal tissue, making boundaries difficult to define by most diagnostic imaging methods, MR imaging is used to define tumor margins and extent. Our research group has developed a high-contrast, high-resolution method for MR imaging of the breast, called RODEO (ROtating Delivery of Excitation Off-resonance), proven to have twice the sensitivity and specificity of mammography. Cellular death induced by ILP produces a phase change that can be visualized on MR images. This MRI hypointense zone can then be used to determine the adequacy of ILP treatment. The combination of RODEO imaging and a system for MRI-directed stereotaxic biopsy allows the accurate localization and placement of the laser fibers for ILP. This study tests the feasibility and outcome of MR-directed ILP in 30 patients with breast cancer who are scheduled for surgical removal of the lesion (mastectomy or lumpectomy). Our major findings to date are (1) RODEO MRI can accurately identify cancers for laser ablation; (2) Stereotaxic MRI needle positioning can be performed; (3) Fast RODEO MRI can accurately depict zones of ablation for interactive ILP; (4) ILP is an effective method for the minimally invasive ablation of breast cancer; (5) MRI-guided ILP is safe and is a potential alternative to surgical lumpectomy; and (6) MRI-guided ILP may have lower costs and provide better cosmesis than surgical lumpectomy.

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(4) TABLE OF CONTENTS

(5) INTRODUCTION

SUBJECT

MR-directed ILP as an innovative alternative to breast conserving surgery.

PURPOSE

To prove that combining minimally invasive treatment (ILP) with the diagnostic accuracy of MR imaging provides a treatment for breast cancer that is vastly superior cosmetically to breast conserving surgery, at a significantly lower cost.

SCOPE OF RESEARCH

1. Demonstrate the potential of ILP for use as a minimally invasive therapy for breast cancer.
2. Demonstrate the capability of MR imaging to accurately localize breast cancer and stereotactically position needles for ILP.
3. Validate with rigorous MR/pathological correlations the capability of breast MR imaging to accurately determine the treatment zone resulting from ILP.

BACKGROUND

Goals of Breast Cancer Therapy

The goals of current breast cancer treatment include early detection while the disease is confined to the breast and local control that results in minimal deformity. Because of the inability to accurately determine the extent of disease before therapy, more extensive treatment is often provided than is actually necessary to cure the disease. This tendency toward over-treatment results in greater morbidity for the patient and high costs for the health care system.

The highly accurate Magnetic Resonance Imaging (MRI) method for breast cancer used by our group was developed with the motivation that better depiction of lesion extent could dramatically improve the treatment of breast cancer. Recent studies demonstrate the capability of interstitial laser photocoagulation (ILP) for the minimally invasive treatment of solid tumors. In conjunction with Fischer Imaging (Denver, CO), we have developed a prototype stereotaxic biopsy table that is specifically designed for accurate MRI positioning. The goal of this research is to combine high resolution MRI definition of cancer extent, accurate stereotaxic MRI positioning, and ILP into an alternative method for breast conservation surgery. The use of this novel treatment approach would vastly improve cosmesis, reduce morbidity, and lower costs, thus eradicating some of the most detrimental effects of breast cancer therapy.

ILP for Cancer Treatment

ILP has recently been used as a minimally invasive treatment for certain solid tumors. It is based upon the local delivery of low level heat (approximately 50°C) over a period of about 10 minutes. A percutaneous approach is used to place a laser fiber within the lesion using imaging guidance [1-10]. The extent of tissue destruction is a function of fiber position and the temperature gradients created with the interaction of the laser and the cellular components of the tissue. The necrotic tissue that is created by ILP subsequently heals by resorption, regeneration, and/or fibrosis [1-10].

In the United Kingdom, approximately 50 patients with breast cancer have been treated on an experimental protocol using ILP with ultrasound guidance [10]. The analysis of the surgical specimens following this treatment showed obliteration of the lesion, demonstrating the effectiveness of ILP for the

treatment of breast carcinoma. However, even though these early results show substantial promise for ILP as a potential treatment alternative for breast cancer, better imaging control than is presently available with sonographic or computed tomographic imaging is needed to determine disease extent and treatment effectiveness [10].

Unlike many solid tumors that have a well-defined interface with adjacent normal tissues, breast cancer infiltrates the surrounding tissue, making the margin difficult to appreciate on most imaging studies and even at surgery. The heterogeneity of breast tissue makes the theoretical prediction of laser heating effectiveness difficult. The surgical correlate of "free margins", obtained with the analysis of the pathology specimen, is needed to determine when ILP has sufficiently destroyed the tumor, leaving a margin of normal tissue. Recent studies have determined that MRI can identify the zones of regional heating resulting from ILP [11-14]. The cellular death induced by ILP produces a phase change that can be visualized on MR images. This MRI hypointense zone can be used to determine the adequacy of ILP treatment of breast cancer and directly define the extent of cell death. The most important role of MR in this setting is the ability to accurately define tumor and treatment margins.

MR Imaging

A high contrast, high resolution MR imaging method called RODEO (ROtating Delivery of Excitation Off-resonance) was developed by our group specifically for breast cancer imaging. Since the introduction of this new imaging technique in 1991, over 1200 breast examinations have been performed by our research group. This breast MRI experience constitutes one of the world's largest series employing consistent MRI technology and represents the only large series of MRI/serially sectioned pathology correlations. Correlation with rigorous pathological analysis in over 400 serially sectioned mastectomy specimens has validated the accuracy of this method in demonstrating the extent of breast cancer. The sensitivity (94%) and specificity (66%) of RODEO breast MR were twice that of conventional breast imaging when the same cases were evaluated by readers who were blinded to the results of the other examination. In addition, the demonstration by MR imaging of additional, undetected disease foci in 38% of breasts closely approximates the reported prevalence of "subclinical" disease that is reported in rigorous pathological analyses. RODEO imaging can equally detect invasive carcinoma as well as ductal carcinoma *in situ* [24-29]. The remarkable ability of MR imaging to detect tumor margins and extent of disease indicates its potential for successful imaging control during ILP [15-29].

Stereotaxis

Mammographically directed stereotaxic biopsy has become a recognized alternative to surgical biopsy for certain cases of breast cancer, with stereotaxic biopsy reliability now approaching that of surgical biopsy [30-32]. A variety of prototype stereotaxic devices have been built for MR-directed breast biopsy and needle localization [33-38]. These devices generally consist of components that provide breast immobilization, lesion localization, translation of MR imaging coordinates to spatial coordinates, and needle guidance. Since corrections for gradient nonlinearity are needed for accurate needle localization, all methods use some form of fiducial markers that reference the biopsy system to the MR coordinate system. This enables the accurate positioning of needles in three dimensions for subsequent treatment of the lesion using ILP.

MR control of ILP therapy for breast cancer

The current surgical approach for breast conservation in the treatment of breast cancer, lumpectomy followed by analysis of the specimen and possible re-excision, requires several days of hospitalization for completion. Pathological analysis is used to determine the adequacy of the surgical resection. Often (40-70% of cases), the presence of positive margins associated with the lumpectomy specimen requires

additional surgery, either re-excision or mastectomy [39-43]. A Japanese study employing rigorous pathological analysis demonstrated a 95% positive margin rate in simulated lumpectomies [44]. In addition, incomplete tumor excisions and residual microscopic carcinoma may be associated with higher recurrence rates, as suggested by the tendency of larger tumors to recur more frequently [43].

MR-guided ILP, on the other hand, could be vastly more efficient and effective, involving only 2 hours of the patient's time for complete obliteration of the tumor. ILP offers a minimally invasive treatment for breast cancer while MRI accurately defines cancer extent and determines the zone of cellular death. In addition, stereotaxis MRI positioning provides the degree of accuracy needed for insertion of the laser and eliminates the need for beast compression. This unique combination of

insertion of the laser and eliminates the need for breast compression. This unique combination of

better cosmesis, and removal of the discomfort of breast compression, while, at the same time, lowering health care costs through less surgery and hospitalization time. For the patient with breast cancer, this means that local anesthesia and a needle puncture could replace the current regimen of surgery, hospitalization, general anesthesia, recovery, and breast deformity.

Our study tests the feasibility and outcome of MR-directed ILP in 30 patients with breast cancer who are scheduled for surgical removal of the lesion (mastectomy or lumpectomy). We expect our results will indicate that MR-directed ILP is a minimally invasive alternative to breast cancer surgery that can significantly reduce the costs of treatment by eliminating the need for surgery, hospitalization, and anesthesia, while eradicating the deformity resulting from breast surgery and changing the societal perception of breast cancer treatment.

(6) BODY

EXPERIMENTAL METHODS AND PROCEDURES

We currently have funding to conduct breast MR examinations in a series of patients who have suspicious mammographic or clinical findings. A series of 30 patients who are planning to undergo surgery for removal of the lesion will be selected from this existing study for participation in the proposed trial. Entrance criteria include:

1. Focal lesion on MRI with a maximum lesion diameter of 1.5 cm (may be associated with other lesions, but for the purposes of this pilot study, only one lesion will be treated with MR-guided ILP).
2. No previous radiation therapy to the breast.
3. No previous surgery on the lesion to be treated.
4. No contraindications to MR imaging or gadolinium contrast agent.

Patients will be paid $300 for participation in this study.

Stereotaxis

Patient positioning and breast stabilization are essential for obtaining accurate stereotaxis and, thus, successful implementation of MR-guided ILP.

A commercial prototype MR imaging stereotaxic localization and biopsy unit manufactured by Fischer Imaging (Denver, CO) will be utilized for this study. The expertise of Fischer Imaging, the original manufacturer of stereotaxic mammography systems, has been used for the development of this unit, which exploits the unique advantages of MR imaging and eliminates some of the undesirable features of mammography-directed stereotaxis. Fischer has replaced the existing table (General Electric, Milwaukee, WI) with a table constructed from non-ferromagnetic composite material, which allows access to the entire breast from below. The Fischer device is designed for the highly accurate placement of needles and localization wires using a sophisticated c-arm. This allows fast, accurate placement of needles and localization wires at multiple locations. The c-arm approach is unique for MR imaging localization and allows flexibility in the selection of approaches so that the needle tract can be included in the operative field.

In conjunction with this prototype unit, thermal setting plastic will be used to achieve breast stabilization as an alternative to breast compression, which is employed by mammography and most other MRI stereotaxis systems. The thermal setting plastic is highly flexible when warmed and can adopt a shape that is individual for each breast. When the plastic cools to room temperature, it forms a rigid exoskeleton around the breast that facilitates consistent positioning for stereotaxis. This innovative approach to breast stabilization eliminates the need for painful breast compression, a frequently cited problem of mammography.

MR Imaging

All studies will employ a high resolution, high contrast RODEO pulse sequence that has the capability of accurate tumor localization based upon validation by over 400 serially sectioned pathology specimens. MR compatible localization wires and biopsy needles are supplied by EZM (Westbury, NY).

After the patient has been positioned on the table and the breast has been stabilized with the thermal setting plastic, pre- and post-contrast 128-slice RODEO scans will be obtained for localization. Gadopentetate dimeglumine will be used as the contrast medium and will be administered as an intravenous bolus at 0.1 mmol/kg (8-16 ml). Fiducial markers will be used to correct for gradient nonlinearity of the MR imaging coordinates, providing 3D markers for localization and subsequent

positioning of the needle. While remaining in position on the stereotaxic table, the patient will be moved to the front of the magnet where the stereotaxic c-arm is located. The patient will then receive a local anesthetic, and, using the c-arm, a needle will be placed into the center of the lesion. A laser fiber will then be inserted into the needle to the center of the projected treatment zone.

ILP

After the laser fiber has been successfully placed, the patient will be returned to the magnet center, and laser ablation will begin. The ILP therapy will closely follow the methods used by Bown et al [1-3, 10]. A Nd-YAG laser will be used at a power of 1-2 Watts, providing a temperature of about 50°C. The treatment will last approximately 10 minutes, but total treatment time will be determined by the hypointense zone that is seen on MRI.

During laser ablation, MR scans will be obtained at 2-minute intervals using rapid 32-slice acquisitions. During heating, a zone of hypointensity will appear on the MR images around the laser tip due to the phase change resulting from the cellular death. When this hypointense zone adequately covers the post-contrast tumor image as well as an adequate disease-free margin, the heating will be discontinued.

MR/Pathology Correlations

At the conclusion of ILP therapy, the patient will again be moved from the magnet center to the stereotaxic c-arm at the front of the magnet. Using the c-arm, localization wires will be placed at the margins of the hypointense region. These will be used as boundary markers of the treatment zone for subsequent histopathology examination. At least two wires will be used to mark the maximum dimensions of the treatment zone. A repeat MR examination will be performed to confirm the wire position. The patient will then undergo surgery, either lumpectomy or mastectomy, for removal of the lesion. Pathology examination of the excised tissue will be used to determine the position of the localization wires relative to the zone of cellular death.

The proximity of the wire to the tumor and zone of cellular death will be measured in millimeters on the histology slide. The nature of the boundary zone will be analyzed to determine the significance of the MRI signal pattern. The extent of cellular destruction relative to the laser tip will be analyzed and compared to data we have obtained from animal models. Thorough pathological analysis of the specimen will be performed to evaluate potential skip areas, and the consistency, distribution, and effectiveness of ILP will be determined.

Data Analysis

ILP therapy: The capability of ILP as a method for the minimally invasive treatment of breast cancer will be measured by rigorous pathological analysis of the surgical specimen. Either the lumpectomy or the mastectomy specimen will be serially sectioned with liberal histological sampling. The tissue will be analyzed for the location and extent of charring, cellular destruction, and hemorrhage relative to the position of the laser fiber and the margins of the hypointense MRI zone. In particular, we will evaluate the consistency of the laser effect and the potential for asymmetric or skipped areas. These data will be compared to previous results from animal model studies performed in our laboratory and to results reported in the literature. The data will be used to validate the ability of ILP to effectively destroy breast cancer cells *in vivo* and leave a disease-free margin.

MRI localization for stereotaxis: MR images will be interpreted prospectively by the PI, and stereotaxic positioning will be performed based upon this interpretation. At the end of the study, the ability of radiologists to interpret the MRI information for ILP treatment positioning will be evaluated retrospectively. To test the reliability of MRI for lesion identification and localization, three radiologists

who are blinded to the initial location selection will be asked to select a position for centering the laser. The variability and accuracy of selection of the three radiologists will then be determined retrospectively.

MRI treatment control: The MR images that are obtained during ILP will be interpreted prospectively by the PI to determine when an adequate hypointense zone is achieved. To test the capability of radiologists to consistently interpret these data, three radiologists will be asked to retrospectively define the hypointense zone on the final set of treatment images. The accuracy and variations among radiologists will be determined using the pathology gold standard. The histological and biochemical changes in the pathology specimen will be analyzed and correlated with the location of the MRI signal changes and the location of the laser fiber tip. The questions we hope to answer are:

Can MRI detect asymmetric heating or potential skip areas?

What is the histological appearance of the boundary zone?

Is MRI an adequate control method for ILP?

RESULTS AND DISCUSSION

In the proposal, a total of 30 patients were to be treated over three years. To date in Year 1, 10 patients have been treated with 15 applications of MRI-guided interstitial laser photocoagulation. Of these patients, 7 have undergone surgical removal of the area. Of the three patients who have not had surgery, two are scheduled for surgery. One has refused surgery since the ILP procedure ablated all of her tumor, and her tumor was benign. All procedures were well tolerated by the patients. In the first patient, IM Demerol was used in preparation for potential anxiety and/or pain. This patient felt that the procedure did not warrant narcotics. Subsequent patients were given oral Xanex 0.5 mg prior to the procedure in addition to local anesthesia. The procedure had no significant complications, such as infection or hematoma. One patient with a fibroadenoma could not be adequately penetrated by the MRI-compatible 18-guage needle. A 14-guage trucut needle with an introducer was used to gain access to the center of the lesion. Because the larger needle did not fit the fiberoptic as well, a chimney effect resulted in some skin burning (about 5 mm diameter) at the entry site. This patient did not go to surgery, but the small skin burn resolved at 4 weeks post-procedure. The following is a summary of the findings to date.

Sterotaxis

The MRI stereotaxic device from Fischer Imaging has been delayed due to the need for equipment modifications. The study was initiated with a device from MRI Devices, Inc. This device is now commercially available and being used in the ongoing NCI sponsored multicenter trial. This device has lower accuracy than the Fischer unit but was adequate for needle placement for a single fiber. We are now using the modified Fischer unit, which is accurate to within 0.5 mm and allows the rapid placement of multiple fibers. We have demonstrated the accuracy of stereotaxic MRI for the placement of needles for ILP.

The MRI-compatible needles from EZM have worked adequately. The major problem is that the artifact from the metal obscures a portion of the ablation zone. Once the fiber is in place, the needle can be slipped back to leave a bare fiber in the lesion. This manipulation eliminates the artifact problem but could potentially move the fiber tip from the desired position. We are going to receive some prototype carbon-based needles from EZM that have no MRI artifact.

MR Imaging

The RODEO pulse sequence has accurately identifed the cancers and margins in all cases [15-25]. Fast 1-minute RODEO images (32 slice 3D acquisitions) have accurately depicted the hypointense

ablation zone in all cases. At the end of the treatment, a high resolution post-contrast RODEO is used to measure the ablation zone in three dimensions.

New imaging technology is being developed for faster image acquisition and higher contrast.

Interstitial laser photocoagulation

The Nd-YAG laser has been replaced with a diode laser (Diomed, Cambridge, UK). The diode laser has a similar wavelength (805 nm) and can be split into four separate fibers for treating a larger area. After placement of the fiber, the fiber tip is pre-charred with 25 watts of power for 3 seconds. Subsequently, the power is reduced to 3 watts for a duration of about 10 minutes. This method has been widely employed by Bown et al [1-10]. The laser position and duration is interactively controlled by the fast RODEO images that are obtained during the ablation.

MR/Pathology correlation

Of the patients that have undergone surgery, two have had mastectomies with serial pathologic sectioning. This method employs chilling of the breast tissue until firm and subsequent sectioning of the tissue at 5-mm increments. This method has been adopted by the International Breast MRI Consortium as a gold standard for accuracy measurement of breast MRI [15]. The remaining five patients had lumpectomies with sectioning of the lumpectomy specimen at 5-mm increments. The size of the ablation zone is measured grossly and with the use of a UV lamp. Ample histologic sectioning of the area of treatment is used to measure the potential for ablation zone irregulatities or skipped regions. The PCNA stain is used to demonstrate the lack of DNA replication as a signature of cellular death that cannot be seen on standard H&E stains. The PCNA stain can show the ablation zone within one hour after ILP. The size of the ablation zone for correlation with MRI is measured on a PCNA-stained section cut through the center of the ablation zone. In all cases, the ablation zone size has correlated within 1 mm with the MRI depicted area of hypointensity. No skip areas have been found within the ablation zone. The placement of wire markers for ablation zone marking has not been possible due to inaccuracies in the stereotaxic device. With the recent integration of the Fischer device, we plan to institute ablation zone marking with wires before surgery.

SCHEDULED PRESENTATIONS

1. Harms SE, Mumtaz H, Klimberg S, et al. Laser lumpectomy with interactive MR imaging: histopathologic correlation. Radiological Society of North America, 1998 (accepted).
2. Harms SE. MRI guided therapy. Miami Breast Conference, 1999 (accepted).
3. Harms SE, Mumtaz H, Klimberg S, et al. MRI guided laser lumpectomy MRI guided laser lumpectomy. San Antonio Breast Conference, 1998 (submitted).

PUBLICATIONS

1. Harms SE, Mumtaz H, Klimberg S, Westbrook K. RODEO guided laser lumpectomy. Breast Diseases: a Year Book Quarterly (submitted).

(7) CONCLUSIONS

Preliminary results would indicate that:

1. RODEO MRI can accurately identify cancers for laser ablation.
2. Stereotaxic MRI needle positioning can be performed.
3. Fast RODEO MRI can accurately depict zones of ablation for interactive ILP.
4. ILP is an effective method for the minimally invasive ablation of breast cancer.
5. MRI-guided ILP is safe and is a potential alternative to surgical lumpectomy.
6. MRI-guided ILP may have lower costs and provide better cosmesis than surgical lumpectomy.

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